MATERIALS TRANSFER AGREEMENT

Provider:

U.S. Environmental Protection Agency, National Center for Computational Toxicology

Recipient:

Solidus Biosciences, Inc.

1. Provider agrees to transfer to Recipient's Investigator named below the following Research Material:

> A copy of the ToxCast™ chemical library consisting of 50 microliters each of 320 chemical samples prepared as solutions in dimethyl sulfoxide at a concentraton of 20 millimolar.

2. This Research Material may not be used in human subjects. The Research Material will be used only for research purposes by Recipient's investigator in his/her laboratory, for the research project described below, under suitable containment conditions. Recipient agrees to comply with all Federal rules and regulations applicable to the Research Project and the handling of the Research Material.

2(a). Were Research Materials collected according to 45 C.F.R. Part 46, "Protection of Human Subjects?"
___ Yes (Please provide Assurance Number:_____)
___ No
_X_ Not Applicable (Materials not collected from humans)

3. This Research Material will be used by Recipient's investigator solely in connection with the following research projects described with specificity as follows *(use an attachment page if necessary)*: In collaboration with EPA, investigate and characterize the effects of these compounds on cytotoxicity on cell lines using the MetaChip and/or DataChip high-throughput cytotoxicity systems. These systems would evaluate the IC50 of the parent compound vs. the compound after biotransformation induced by some combination of the following systems:

1. Control
2. CYP450 mixtures
3. Phase II enzyme mixtures
4. CYP450 and Phase II enzyme mixtures

4. In all oral presentations or written publications concerning the Research Project, Recipient will acknowledge Provider's contribution of this Research Material unless requested otherwise. To the extent permitted by law, Recipient agrees to treat as confidential, any of Provider's written information about this Research Material that is stamped "CONFIDENTIAL" for a period of five (5) years from the date of its disclosure to recipient. The foregoing shall not apply to information that is or becomes publicly available or which is disclosed to Recipient without a confidentiality obligation. Any oral disclosures from Provider to Recipient which Provider wishes to be treated as confidential shall be identified as being Confidential at the time of the disclosure and by written notice delivered to Recipient within thirty (30) days after the date of the oral disclosure. Recipient may publish or otherwise publicly disclose the results of the Research Project, but if Provider has given Confidential information to Recipient, such public disclosure may be made only after Provider has had thirty (30) days to review the proposed disclosure to determine if it includes any Confidential information, except when the shortened time period is pursuant to a court order or to the extent such review period is permitted by law.

5. The Recipient will provide to the Provider all testing results obtained by the Recipient using the Research Material. Recipient acknowledges that the Provider will make such testing results freely available to the public.

6. This Research Material represents a significant investment on the part of Provider and is considered proprietary to Provider. Recipient's investigator therefore agrees to retain control over this Research Material and further agrees not to transfer the Research Material to other people not under his/her direct supervision without advance written approval of Provider. Provider reserves the right to distribute the Research Material to others and to use it for its own purposes. When the Research Project is completed, the Research Material will be returned to the Provider or disposed, if directed by Provider.

7. This Research Material is provided as a service to the research community. It is being supplied to Recipient with no warranties, express or implied, including any warranty of merchantability or fitness for a particular purpose. Provider makes no representations that the use of the Research Material will not infringe any patent or proprietary rights of third parties.

8. Recipient shall retain title to any patent or other intellectual property rights in inventions made by its employees in the course of the Research Project. However, if said inventions contain any portion of the Research Material, are derived from the Research Material, or could not have been produced but for the use of the Research Material, Recipient agrees to contact the Provider to determine what ownership

interests, if any, the Provider may have, and, where applicable, to negotiate in good faith the terms of a commercial license. Inventorship for a patent application or a commercialized product based on said inventions shall be determined according to United States patent law.

9. When Provider is the EPA: Recipient agrees not to claim, infer, or imply endorsement by the Government of the United States of America (hereinafter referred to as "Government") of the Research Project, the institution or personnel conducting the Research Project or any resulting product(s). Recipient agrees to hold the Government harmless and to indemnify the Government for all liabilities, demands, damages, expenses and losses arising out of Recipient's use for any purpose of the Research Material.

10. When Recipient is the EPA: Provider will not be liable to EPA for any claims or damages arising from EPA's use of the Research Material.

11. This Agreement shall begin on the date of its execution and continue for twelve (12) months thereafter, and shall automatically renew for successive year long periods (a) unless one party notifies the other party no sooner that thirty (30) days prior to such renewal date that it elects not to renew the Agreement, or (b) unless earlier terminated as provided in the next sentence. The Provider shall have the right to terminate this Agreement at any time if Recipient breaches any of the terms of this Agreement. Upon termination, Recipient shall return to the Provider all unused portions of the Research Materials.

12. All notices pertaining to or required by this Agreement shall be in writing and shall be signed by an authorized representative and shall be delivered by hand (including private courier mail service) or sent by certified mail, return receipt requested, with postage prepaid, addressed as follows:

Provider's Official and Mailing Address:

Robert J. Kavlock, Director
National Center for Computational Toxicology (NCCT)
US EPA (MD-205-01)
4930 Old Page Rd.
Research Triangle Park, NC 27711

Recipient's Official and Mailing Address:

Dr. Jonathan Dordick, President
Solidus Biosciences, Inc.1223 Peoples Avenue

Any false or misleading statements made, presented, or submitted to the Government, including any material omissions, under this Agreement and during the course of negotiation of this Agreement are subject to all applicable civil and criminal statutes including 31 U.S.C. ' ' 3801-3812 (civil liability), 18 U.S.C. ' 1001 (criminal liability), and 31 U.S.C. ' ' 3729-33 (False Claims Act).

NCCT Project IIC-4 (FY2006 Implementation Plan)
Title: ToxCast, a Tool for Categorization and Prioritization of Chemical Hazard Based on Multi-Dimensional Information Domains.
Research Issue and relevance: Across several EPA Program Offices (e.g., OPPTS, OW, OAR), there is a clear need to develop strategies and methods to screen large numbers of chemicals for potential toxicity, and to use the resulting information to prioritize the use of testing resources towards those entities and endpoints that present the greatest likelihood of risk to human health and the environment. This need could be addressed using the experience of the pharmaceutical industry in the use of advanced modern molecular biology and computational chemistry tools for the development of new drugs, with appropriate adjustment to the needs and desires of environmental toxicology. A conceptual approach named ToxCast has been developed to address the needs of EPA Program Offices in the area of prioritization and screening.
Approach: Modern computational chemistry and molecular biology tools bring enabling technologies forward that can provide information about the physical and biological properties of large numbers of chemicals. The essence of the proposal is to conduct a demonstration project based upon a rich toxicological database (e.g., registered pesticides, or the chemicals tested in the NTP bioassay program), select a fairly large number (50-100 or more chemicals) representative of a number of differing structural classes and phenotypic outcomes (e.g., carcinogens, reproductive toxicants, neurotoxicants), and evaluate them across a broad spectrum of information domains that modern technology has provided (i.e., physical-chemical properties, predicted biological activities based on existing structure-activity models, biochemical properties based on high throughput screening assays, cell based organotypic assays, and genomic analysis of cells or organisms). These domains represent increasing biological relevance, as well as increasing resource requirements. The ultimate goal of the project would be to mine the resulting data for association between and among the various domains and the known toxicological properties of the base set of chemicals in order to provide a structured strategy to identify potential toxicity pathways, and to prioritize chemicals them for subsequent testing based on that information.

The underlying hypothesis is that whether concerned with the off target effects of drugs, as desired to be understood by the pharmaceutical industry, or toxicity in case of environmental agents of interest to the EPA, the response is driven by interactions with biomolecular targets of one form or another. One needs only to identify those receptors of concern and identify tools for assessing the likelihood of interaction with the chemicals of concern. In moving from the drug development arena (which can be compared to working along one or just a few vectors) to the environmental toxicology arena (which can be likened to working on a matrix instead of a vector), one needs to shift from a specific screening target to a more global agenda, and it becomes necessary to vastly expand the number of potential biomolecular targets, be these

obtained from *in silico* assays, biochemical assays, cell based *in vitro* assays, surrogate animal models, or short term studies in traditional species. Hence, a wider net of endpoints and information sources will be applied, at least initially, as the concept transgresses from a concept to a reality.

A number of hurdles would need to be addressed before launching such an effort, including: (1) identification of a subset of chemicals for serving as the proof of concept models; (2) developing a chemical inventory management and distribution system; (3) identifying an upper cap on the per chemical cost of obtaining screening level data: (4) selecting assays within the available resources; (5) flexibility, or tiering, of domains based upon pre-existing knowledge; (6) perhaps initially targeting only a few manifestations of toxicity rather the all possible ones to decrease the complexity of the task; (7) evaluating the impact of metabolizing capability, or lack thereof, on the efficiency of the screening assays; (8) developing a bioinformatic approach to mining the resulting data and identifying signatures of concern; and (9) carrying out a prospective assessment of the bioinformatic approach using chemicals currently entering a traditional testing process. These hurdles would be the subject of considerable discussion as the potential feasibility of this concept proposal is discussed further.

Progress to date: At this point in time, ToxCast is nearly at the end of its conceptual design phase. The information domains have been identified, and a number of potential contributing data sources have been investigated. Recruitment actions are underway to add two staff members to the NCCT who will be responsible for the biological and information processing components of ToxCast. Communications have been established with the NTP/NIEHS which has similar interests and which is beginning to work with the NIH Molecular Libraries Initiative (see also the DSSTox implementation plan). Outreach to the OPPTS, ACC, EDF and other external groups has also begun to help develop a consensus on the specific directions and contents of ToxCast.

Impact: The availability of a biologically and chemically based system to begin to associate chemicals of like properties and activities will provide a number of EPA Program Offices with an extremely useful tool that heretofore has been seriously lacking. The tool may be one of the first broad scale products of the NCCT that addresses the mission of improving the efficiency and effectiveness of hazard identification and risk assessment methodologies employed by the EPA.

Partnerships/collaborations: The NCCT is working to establish partnerships with a number of external groups that can facilitate development of the information needed in ToxCast. These groups include the OPPTS, the NTP/NIEHS, the ACC, the EDF and a number of commercial vendors that market some of the enabling technologies.

Milestones/products

FY05 - Develop conceptual framework for ToxCast

FY06 - Establish initial battery of assays across the information domains,

identify list of chemicals to evaluate proof of concept for framework and begin data acquisition
FY07 - Report on the utility of statistical clustering techniques on assay results from pilot chemicals to group them according to known toxicity patterns; revise framework as dictated by results

NCCT Project IIID-7 (FY2006 Implementation Plan)
Title: Developing Computational Tools for Application of Toxicogenomics to Environmental Regulations and Risk Assessment

Research Issue and Relevance: Toxicogenomics is the study of changes in gene expression, protein, and metabolite profiles within cells and tissues, complementary to more traditional toxicological methods. Genomics tools provide detailed molecular data about the underlying biochemical mechanisms of toxicity, and could represent sensitive and precise approaches for detecting effects of exposures, or methods for comparing these effects between species or individuals. Thus genomics, proteomics and metabonomics can provide useful weight-of-evidence data along the source-to-outcome continuum, when appropriate bioinformatic and computational methods are applied towards integrating molecular, chemical and toxicological information. The *Interim Policy on Genomics* (http://www.epa.gov/osa/spc/genomics.htm) recognizes that if genomics is to become useful in regulatory decision-making, risk assessment, and environmental monitoring, the Agency will require the computational methods to handle such data. Measuring changes in gene expression using DNA microarrays has proven useful for identifying biological processes and informing hazard identification and mode of action in toxicological research. Similar microarray data have already arisen in Agency environmental decision-making, and regulatory applications of genomics are likely to increase. EPA's Science Policy Council (SPC) paper on the *Potential Implications of Genomics for Regulatory and Risk Assessment Applications at EPA* (http://www.epa.gov/osa/genomics.htm) highlights the potential of toxicogenomics in chemical prioritization and risk assessment. To realize this potential, EPA must have the ability for proper analysis and storage, as well as the computational tools to incorporate these types of data into regulatory decisions. Development of these databases and tools, and application of these various toxicogenomic data within Program and Regional Offices will provide EPA staff with valuable, practical training in genomics and associated disciplines. As toxicogenomics grows more important to environmental science and policy, the NCCT will help EPA develop the computational tools and methods to properly evaluate genomics information

Approach: To address the need for development of tools for managing and analyzing toxicogenomics data, the National Center for Computational Toxicology (NCCT) is working across the Office of Research and Development (ORD), the Program and Regional Offices of EPA, and with other Federal and extramural partners. The NCCT is coordinating it's toxicogenomics efforts with the rest of the Agency through the SPC's Genomics Technical Framework and Training Workgroup. This Workgroup has drafted an *Interim Guidance for Microarray-Based Assays: Regulatory and Risk Assessment Applications at EPA,* that recommends continued collaboration with other federal agencies and stakeholders in developing management and analysis tools for genomics

data, and the execution of a series of case studies of genomics applications to chemical prioritization or risk assessment. The NCCT intends to follow these recommendations through a series of projects and partnerships within the Agency, and with the FDA and the STAR-funded Environmental Bioninformatic Centers (EBC) in NC and NJ.

First, the NCCT will develop a federated database(s) and analytical tools for the management and analysis of toxicogenomic data for both research and regulatory applications. This project was initiated in FY2006, and is building on the success of FDA's ArrayTrack database. It is NCCT's goal that this effort provides a complete data management solution that addresses requirements unique to scientifically-based risk assessments, confidential and proprietary data security, public access, and other aspects of regulatory application. Consistency, scientific and operational robustness, common access, and availability in a scalable environment are all part of these data management requirements. The expected result is an Agency-wide data management solution integrating genomics, toxicological, and other key data required for both research and regulatory applications. This EPA database containing gene expression profiles and toxicological data for a wide variety of chemicals will facilitate creation of the statistical and computational methods for predictive toxicology. As part of this effort to develop microarray and toxicogenomic analysis tools, the NCCT is continuing to participate in the Microarray Quality Control (MAQC) project. The MAQC is a comprehensive study of microarray quality control and cross-platform comparison, executed by a consortium of many commercial, government (FDA, EPA, NIST, NIH), and academic participants. The MAQC objectives include measuring intra-platform performance; inter-platform comparability; relative accuracy; and concordance of expression measurements to other technologies (e.g. TaqMan PCR).

The second part of NCCT efforts in toxicogenomics are a series of specific, model applications of toxicogenomics data to environmental chemical prioritizations or risk assessments. This includes some of the toxicogenomics elements of the ToxCast program for chemical prioritization, that are generating genomics and metabolomics data from cell cultures which can be loaded into the EPA toxicogenomics database. Also, toxicological data from EPA Program Offices for pesticides and other environmental chemicals will be captured into the toxicogenomic database for use for both chemical prioritization efforts (i.e., ToxCast) as well as risk assessment applications of toxicogenomics. Additional risk assessment applications of toxicogenomics data include ORD-wide work on the conazole fungicides cancer and non-cancer mode(s) of action; pyrethroid pesticides neurotoxicity; perfluorylalkyl acids (PFAA) developmental and hepatotoxicity; the antiandrogenicity of phthalates; the immunotoxicity of diesel particles; and the role of urban air particles in asthma. The NCCT will coordinate across ORD and the Program and Regional Offices, as well as with the EBC in NC and NJ, on how to manage and analyze these datasets in ways that maximize their utilization in risk assessments.